PATENT

Attorney Docket No. 001-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: C. Smith
Michael D. Doyle et al.	Art Unit: 1631
Application No.: 09/916,709	APPELLANT'S BRIEF UNDER 37 C.F.R. § 41.37
Filed: 07/27/2001	
For: METHOD AND SYSTEM FOR THE MULTIDIMENSIONAL MORPHOLOGICAL RECONSTRUCTION OF GENOME EXPRESSION ACTIVITY	

Commissioner for Patents

Sir:

The following is appellant's Appeal Brief submitted pursuant to 37 CFR 41.37(a). Appellants reserve the right to request an oral hearing pursuant to 37 CFR 41.47 following receipt of the Examiner's Answer.

REAL PARTY IN INTEREST:

The named inventors are the real party in interest as the owners of the above-identified application.

RELATED APPEALS AND INTERFERENCES:

No other appeals or interferences are known which will directly affect or be affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS:

Claims 1-4, 6, 7 and 9-11 remain pending in this application and have been finally rejected. Appellant appeals the final rejection of claims 1-4, 6, 7 and 9-11.

STATUS OF AMENDMENTS:

A Rule 116 amendment correcting typographical errors and putting the claims in condition for appeal is filed herewith.

SUMMARY OF THE CLAIMED SUBJECT MATTER:

CLAIM 1

The subject matter recited in claim 1 includes the steps cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7 line 33 to page 8, line 5), and assigning unique codes to each of the micro dissected section samples that indicate tissue space coordinates of the micro dissected sections samples in the multidimensional morphological matrix of image data (Application at page 8 lines 8-10).

Each coded incised section sample is analyzed to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24). This biological data is spatially mapped onto the multidimensional morphological spatial matrix to superimpose the biological data upon volume image data indicated by the code assigned to the coded micro dissected section sample (Application at page 8, lines 26-34).

CLAIM 4

The subject matter recited in claim 4 includes the steps of cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), histologically staining and coverslipping a first set of serial samples for light microscopy (Application at page 7, lines 25 and 26); constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), mounting and covering a second set of serial sample sections with a micro dissection membrane (Application at page 7, lines 27-28), unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7 line 33 to page 8, line 5), providing a set of coded micro dissected section sample holders, with each coded micro dissected section sample holder having a code indicating a unique tissue space coordinate in the multidimensional morphological spatial matrix of image data (Application at page 8, lines 6-9), transferring each micro dissected section sample to a coded micro dissected section sample holder having a code indicating the location of a transferred micro dissected section sample in the multidimensional morphological spatial matrix of image data (Application at page 8, lines 6-9).

Each coded incised section sample is analyzed to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample

(Application at page 8, lines 16-24). This biological data is spatially mapped onto the multidimensional morphological spatial matrix to superimpose the biological data upon volume image data indicated by the code assigned to the coded micro dissected section sample (Application at page 8, lines 26-34).

CLAIM 7

The subject matter recited in claim 7 includes the steps of cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7 line 33 to page 8, line 5).

Each coded incised section sample is analyzed to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24). This biological data is linked to the location in the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample (Application at page 8, lines 26-34).

CLAIM 11

The subject matter recited in claim 7 includes means for of cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), means for constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), means for unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7 line 33 to page 8, line 5), means for analyzing each coded incised section sample to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24), and means for linking this biological data to the location in the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample (Application at page 8, lines 26-34).

GROUNDS OF REJECTION:

I. New Matter

Claims 1-4 and 6 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

II. Indefiniteness

Claims 1-4, 6, 7, and 9-11 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

III. Obviousness

Claims 1-3, 6, 7, and 9-11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Heppelmann et al. (Journal of Microscopy, Vol. 156, Pt. 2, 1989, pages 163-172) in view of Cole et al. (Nature Genetics supplement, Vol. 21, 1991, pages 38-41), Farr et al. (P/N 5,811,231), Emmert-Buck et al. (Science, Vol. 274, 1996, pages 998-1001), and Lemelson (P/N 6,058,323).

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Heppelmann et al. (Journal of Microscopy, Vol. 156, Pt. 2, 1989, pages 163-172) in view of Cole et al. (Nature Genetics supplement, Vol. 21, 1991, pages 38-41), Farr et al. (P/N 5,811,231), Emmert-Buck et al. (Science, Vo. 274, 1996, pages 998-1001), and Lemelson (P/N 6,058,323) as applied to claims 1-3, 6-7, and 9-11, and additionally in view of Bogen et al (P/N 6,281,004).

III. Informalities.

Informalities objected to in claim 4 are corrected in the attached amendment.

ARGUMENT:

1. Summary of the Argument

I. No new matter has been introduced into the claims in the amendment filed November 28, 2005. The phrases pointed out by the examiner are clearly supported by the disclosure of the originally filed application.

II. The pending claims particularly point out and distinctly claim the subject matter which the applicant regards as his invention and are not indefinite. The phrases pointed out by the examiner are not indefinite when read in light of the disclosure and level of skill in the art.

The phrase "based on" in claims 7, 9, 10, and 11 has been replaced by -- from -- to provide clearer wording as requested by the examiner. Claim 4 has previously been amended to make this change and the change was accepted by the examiner.

II. The subject matter recited in the pending claims would not have been obvious to a person of ordinary skill in the art at the time the invention was made.

A. All the limitations recited in claims 1 and 4 are not taught by the cited references as required in MPEP §2143.03.

B. The proposed modification would change the principle of operation of the reference in contradiction of MPEP §2143.01.

C. The cited prior art does not suggest the desirability of the claimed combination as required by MPEP §2143.01

2. Statement of the Arguments

I. New Matter

CLAIM 1

The examiner states that there is no adequate written description of the phrase "volume image data indicated by the code assigned to the coded micro dissected section sample" (last two lines of claim 1).

The originally filed application states at paragraph [41]:

> The gene expression data resulting from #4 are then spatially mapped onto the original multidimensional morphological matrix of image data. This is done by setting parameter bits in voxel data, to superimpose the expression message distribution upon the morphological volume image data. The volume image data is correlated with the x, y, z coordinates of the rasterized tissue samples so that the locations of tissue samples are accurately located in the image data. This allows various types of analysis to be performed on the resultant correlated multidimensional spatial datasets. The details of implementing spatial mapping are well-known in the computer arts and not described in detail here.

The gene expression data from #4 refers to the analysis described in [39] where samples are subjected to analysis. The results of the analysis are correlated with the tissue space x,y,z coordinates. As described in [41], the spatial mapping of the gene expression data onto the original multidimensional morphological matrix of image data is done by superimposing the expression message distribution upon the morphological image data. This superimposing is accomplished by correlating the image data with the x,y,z coordinates of the rasterized tissue sample. As set forth in line 14-15 of claim 1, each unique code indicates tissue space coordinates of each coded micro dissected section sample.

Thus, the language objected to in claim 1 is clearly supported by the disclosure of the originally filed specification. The volume image data is indicated by the code, i.e., the tissue space coordinates of the sample, because the image data is correlated with the x,y,z tissue space coordinates.

CLAIM 4

The examiner states that there is no adequate written description of the phrase "superimpos[sic] gene expression data of a micro dissected section sample gri[sic] onto a [sic] spatial coordinate" in claim 4, lines 28-31.

Paragraph [41] of the specification, quoted above, clearly states that the gene expression data, resulting from the analysis described in paragraph [39] that is indicated by the code of the micro dissection sample holder, is spatially mapped onto the original multidimensional morphological matrix of image data. This mapping is done by superimposing the expression message data upon the morphological image data. Since the volume image data is correlated with the x,y,z coordinates of the rasterized tissue samples, the locations of the tissue samples are accurately located in the image data.

Accordingly, the language objected to in claim 4 is clearly supported by the original disclosure of the application. As is made clear in the specification, the micro samples are placed in sample holders having a code comprising tissue space coordinates indicating the location of the sample held in the holder. The gene expression data of the samples is then mapped onto the image data utilizing the codes assigned to the sample holders. And these codes, i.e., tissue space coordinates, are correlated with the volume image data so that the gene expression data can be superimposed onto a spatial coordinate of the image data.

II. Indefiniteness

INDEPENDENT CLAIMS 1, 4, 7, AND 11

The examiner states that the phrase "unattendedly micro dissecting" is vague and indefinite and it is unclear by what or by whom the micro dissecting is being unattended.

The Office Action states, at page 17, that the claims do not recite "without any selection by investigator". However, this is clearly the intent of the phrase "unattendedly micro dissecting". As stated at paragraph [35] of the specification:

> A UV laser of the type described in Cole, et al., [Cole, K.A. et al., Nat Genet, 21(1 Suppl):38-41 (1999)] is used to incise a grid pattern across each tissue section of the uncovered set of alternating serial sections described in #1

> above. This is done with the use of said UV laser adapted to the application end of a microarray-creation robotic apparatus, as described in Cheung [Cheung, V.G., et al., Nat Genet, 21(1 Suppl):15-9 (1999)]. This allows for unattended section incising of a large number of specimens. A second adaptation of the robotic apparatus [Cheung, V.G., et al., Nat Genet, 21(1 Suppl):15-9 (1999)] adds a microdissection-transfer film holder to the application end of the apparatus. (emphasis added)

Accordingly, a concrete example of unattendedly micro dissecting is the use of the robotic apparatus disclosed by Cheung. Other types of unattended microdissection may also be described by the phrase. The use of the adverb "unattendedly" to modify the gerund "micro dissecting" is grammatically correct and the meaning is clear when taking into account the detailed description and examples provided in the specification. The lack of a reference to what or whom the micro dissecting is being unattended does make the claim indefinite. It is clear from the language that the micro dissection of a serial section does not require active selection of parts of the serial section to be micro dissected.

Further, the examiner has consistently objected to any claim language not taken from the specification throughout the prosecution of this application. Thus, it is believed that the inclusion of the phrase "without any selection by investigator" in the claims would lead to a rejection. The phrase "unattendedly micro dissecting" is based on explicit language of the specification and its meaning is clear from that language.

CLAIM 4

The examiner states that the phrase "superrimpose[sic] gene expression data of a micro dissected section sample gri[sic] onto a [sic] spatial coordinate" is vague and indefinite.

The Office Action states that it is unclear if the expression data of a grid is intended to be superimposed on the previously mentioned coordinate or any coordinate.

The language submitted in the response is as follows:

> ~~utilizing the index data to~~ spatially superimpose~~ing~~ gene expression data of ~~each~~ a micro dissected section sample grid ~~element~~ onto the a spatial coordinate of the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample holder holding the micro dissected section sample.

It is clear that it was intended that the term "grid element" be replaced by the term -- micro dissected section sample-- from the context of the claim and the remarks. This language is clarified in the amendment attached to this brief and has no effect on the examiner's analysis of the claims in the remainder of the office action.

It is respectfully requested that the Board consider the clearly intended language of the claim when determining patentability. An amendment clarifying claim 4 is submitted with this brief.

III. Obviousness

INDEPENDENT CLAIMS 1, 7, AND 11

The Cited References

1. Heppelmann

Heppelmann discloses two different techniques for three-dimensional reconstruction of extended fine tissue structures: a re-embedding technique and a serial section-ESI technique. It also describes true-to-scale three-dimensional reconstructions.

In the re-embedding technique, the extended fine tissue structure is cut into semi-thin serial sections and the semi-thin sections are examined under oil immersion and photographed. If a semi-thin section is selected for ultra-structural examination then the semi-thin section is re-embedded and converted into a series of ultra-thin sections for viewing the ultra-structural detail of the tissue within that section. Heppelmann, page 164, Re-embedding technique, first and second paragraphs.

Further, in the serial section-ESI technique, a set of serial sections is cut and analyzed utilizing ESI. Heppelmann mentions cutting a complete set of alternate semi- and ultra-thin sections of a tissue block. However, all of these sections are then mounted, in their entirety, in sequence on a mesh transmission grid and imaged using ESI. Id., page 165, first paragraph.

The result of the Heppelmann product is a series of images of the sections, as depicted on the left side of Fig. 4 of Heppelmann, which can be used to form a 3-D reconstruction, as depicted on the right side of Fig. 4. The serial sections on the left side of Fig. 4 form the x,y planes of the 3-D structure and the location of the sections in the 3-D structure is indicated by a z coordinate.

2. Cole

The reference Cole teaches the use of histologically cut serial sections to precisely identify specific tumor cells within the prostate gland which are then selected and excised for microarray analysis of expression activity.

In Cole, a 3-D representation of a prostate gland is formed by stacking whole-mount transverse sections cut from the sample. Each serial section may be viewed and is annotated to show the locations where cell populations have been dissected and analyzed. By interactively clicking on these annotations the user can query a database for data related to a selected cell population. In Cole the selection of the cells to be analyzed occurs prior to the dissection of those cells, and those cells are a specific subset of the cells that make up the entirety of the prostate tissue contained in the series of transverse sections.

3. Farr

The Farr reference merely shows that one can study specific cells for a set of several biological parameters at once and includes graphs depicting the relative concentration of a specific chemical as a function of various concentrations of another chemical.

4. Emmert-Buck

Emmert-Buck discloses placing a thin transparent film over a tissue section, visualizing the tissue section microscopically, and selectively adhering the cells of interest within the tissue section to the film with a fixed-position, short-duration, focused pulse from an infrared laser. The adhered section is removed from the serial section providing the image data.

5. Lemelson

Lemelson describes the well-known techniques of generating morphological image data described in the background section of the patent application. Scanning signals are generated by well-known scanning devices such as MRI, CAT, or PET, and the scanning signals are computer processed to generate cross-sectional views. The views are analyzed to define the borders of anatomical structures which may be further processed to provide code signals indicative of coordinate locations of these structures. (9:25-43).

The Examiner's Reasoning

The examiner finds appellants' arguments that none of the references disclose the step of unattendedly micro dissecting each serial sample, assigning code, analyzing the sample, and superimposing or linking the biological data unpersuasive. It is stated that Heppelmann et al. recite micro-dissecting serial samples and Emmert-Buck et al. recite the steps including unattendedly micro-dissecting serial samples. (Office Action; page 16); that Lemelson and recites steps of

assigning code; Cole et al. recite steps of analyzing a sample, and Cole et al. and Farr et al. recite steps of superimposing or linking data. It is stated that Emmert-Buck et al., at page 998, third column, first full paragraph and the abstract, describe automatic micro-dissection without manual procedures.

A. **All the Limitations of Claim 1 are not Taught by the Cited References.**

MPEP §2143.03 requires that all claim limitations must be taught or suggested by the cited references.

As set forth below, none of the references suggest or teach the steps recited in claim 1, 4, 7, and 11.

Independent claims 1, 4, 7, and 11 recite features of unattendedly micro dissecting each serial sample into a set of micro dissected section samples, assigning a code to each micro dissected section sample indicating the location of the coded micro dissected section sample in the multi-dimensional image data, analyzing each coded micro dissected section sample to determine biological data characterizing the micro dissected section sample, and superimposing or linking the biological data of the coded micro dissected section sample upon or to volume image data indicated by the code assigned to the coded micro dissected section sample.

These steps are not taught or suggested in the references.

The examiner states regarding Heppelmann that:

> Heppelmann et al. describes cutting the second set of sections (for ultrastructural examination) and mounting them on single-slot grids to be further examined (page 164, last paragraph) which represents creating a grid pattern across each serial section to create a set of incised section samples for each serial section of the second set, as stated in claims 1, 7, and 11. Heppelmann et al. describe the sections were mounted in sequence on mesh grids (page 165, lines 12-14) which is reasonably interpreted to be associating each incised section sample with a unique set of indices as it has grids (x and y coordinates) with each individual sample placed in a known location as stated in claims 1 and 4.

However, in Heppelmann there is no teaching or suggestion of unattendedly micro dissecting a serial section into a set of micro dissected section samples or of assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix. In Heppelmann, incising the serial sections would be contrary to the teaching of the reference since the serial sections are analyzed by a microscope. Incising or micro dissecting the sections would destroy their utility for that purpose.

Further, there is no suggestion of assigning a code to coded micro dissected section samples. In Heppelmann there is no analysis of samples for biological activity and hence no data to be mapped to the spatial image. Accordingly, there is no motivation to assign codes to the micro dissected tissue samples.

With regard to Cole the examiner states:

> Cole et al. describe methods for preparing microarrays from microdissected cells (page 40, col. 1, lines 19-25 and 37-39). Cole et al discuss that the above processes allow for the determination of exact physical relationships between morphological data (one set) on which overlay gene expression data (second set)(page 40, col. 1, lines 14-17 and col. 2, lines 16-24) which represent associating indices from each incised section sample of the second set with indices of the morphological tissue space matrix

However, in the cited sections of Cole et al. there is no discussion or suggestion of micro dissecting a serial section into a set of micro dissected section samples or assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix.

In Cole, it is stated that "8 micrometer serial cut slides are prepared from tissue blocks ... revealing all the normal pathology in the Z direction". Thus, the reference teaches that the specimen can be cut into serial sections. In Fig. 1 various selected sections have been annotated as being of interest. For example, the figure labeled "bird's eye view" depicts the entire structure with multiple transverse views showing areas of anatomical interest. One of these transverse areas is shown in the figure labeled "transverse road map" view with the areas on which experiments have been performed. Note that the transverse section has not been unattendedly micro dissected into a multi-dimensional spatial matrix of coded micro dissected samples as required by claim 1. The

micro dissected samples in Cole are not distributed in a matrix but are distributed according to the selection of the investigator that did the section. Nor was the micro dissection unattended, but areas of interest were selected.

Accordingly, here is no teaching or suggestion in Cole of the claimed step of unattendedly micro dissecting the serial section into a set of micro dissected section samples.

With regard to Emmert-Buck the examiner states:

> Emmert-Buck et al. describe a laser applied to specific locations of the film to procure specifically targeted cells that can then be transferred (abstract, lines 5-9) which suggest incising grid patterns of the tissue and selecting only particular sections.

However, in the cited section of Emmert-Buck absolutely no teaching or suggestion of unattendedly micro dissecting a serial section into a set of micro dissected section samples or assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix.

The techniques of "visualizing the tissue microscopically, and selectively adhering the cell of interest to the film" described in that reference do not suggest or teach the claimed feature.

Further, the first full paragraph at page 998, col. 3 cited by the examiner as disclosing unattendedly micro dissecting must be considered in the context of the paragraph immediately preceding where it is stated that the cells of interest are selectively adhered to the film. The fact that no manual manipulation is required is inapposite to whether the micro dissection is unattended. The reference must be considered in its entirety, including those sections that would argue against obviousness. Panduit Corp. v. Dennison Manufacturing Company, 227 USPQ 337, 345 (CAFC 1985).

With regard to Lemelson, there is no teaching of unattendedly micro dissecting a serial section sample. Lemelson only relates to digital processing of scanned image data.

Therefore, the claimed feature of unattendedly micro dissecting a serial section into a set of micro dissected section samples and assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix is not taught or suggested in any cited reference.

Further, there is no disclosure of the claimed feature of a code assigned to each micro dissected section sample indicating the location of the coded micro dissected sample in the multidimensional matrix.

B. **The Proposed Modification of Incorporating the features of Cole, Emmert-Buck, Farr, and Lemelson into the three-dimensional reconstruction technique of Heppelmann would change the Principle of Operation of Heppelmann.**

MPEP §2143.01 requires that a prima facie case of obviousness is not established if the proposed modification would change the principle of operation of a reference.

The fundamental principal of operation in the re-embedding technique of Heppelmann, the 3-D model of Cole, and the laser capture micro-dissection of Emmert-Buck is that an area of interest is selected from a section being viewed for further analysis.

In contrast, the method recited in claims 1, 4, 7, and 11 works on a fundamentally different principle of operation in that the serial sections of a biological sample are unattendedly micro dissected into serial sections without any selection, and the micro dissected sections are further analyzed. This allows selection of any part of a serial section for further investigation to occur at anytime subsequent to the micro dissecting because the complete data set is available to be mapped onto the multidimensional image matrix. Thus, the present system lends itself to a survey approach rather than a directed selection approach. As described in [35] of the present application this allows for unattended section incising of a large number of specimens.

In contrast, for example, in Cole if an investigator needed data at a location that had not been previously selected, dissected, and analyzed it would be necessary to go back and dissect another cell population for analysis, which might not be possible. That is because in Cole the investigator selects areas of interest for analysis. As described at paragraph [18], describing Cole, of the present application:

> It should be noted that this study focused on only small groups of specific tissue areas, since the microdissection approach requires a skilled operator and is extremely exacting work. Tissue that isn't used for expression analysis is stained for anatomical reconstruction of the gland architecture, rendering it unusable for further expression analysis. Since this approach is targeted to specific areas of the

tissue, it is most useful for specifically targeted studies, and is poorly suited for survey-based exploratory analysis.

In Emmert-Buck the investigator selectively adheres cells of interest to the film.

Further, with regard to Heppelmann, the proposed combination would change the principle of operation of the primary reference and render it inoperable. If the serial section of Heppelmann were micro dissected it could not be used for the next step of ultra-structural analysis since the structure of the serial section would have been destroyed.

C. **There is No Teaching in the References Suggesting the Combination of the References.**

MPEP §2143.01 requires that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching or suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

It has been clearly established above that the claimed features are not taught or suggested by the cited references. However, even if the various features were disclosed, there is no teaching, suggestion, or motivation in the references to combine the features as recited in the pending claims.

The various references have been described in detail above. The Office Action at pages 12-14 lists a series of motivations to combine the various features as recited in the claims. However, none of the listed motivations meet the recited claim limitations. As described above, Heppelmann, Emmert-Buck, and Cole teach away from the steps of unattendedly micro dissecting the section samples. The references Farr, Lemelson, and Bogen are unrelated to the claimed invention.

For example, at page 13 of the Office Action, it is stated that a PHOSA would have been motivated to create tissue sections of Heppelmann, Cole, and Farr with the automated laser capture micro dissection as stated by Emmert-Buck in order to provide ease, precision, and efficiency in a rapid one-step procurement of selected targeted human cells from a section of complex, heterogeneous tissue.

However, this cited motivation actually teaches away from the claimed combination as described above. Unattended micro dissection is not utilized for procurement of selected cells but for a survey approach to the whole tissue section.

Accordingly, none of the references disclose the steps recited in independent claims 1, 7 and 11 and a *prima facie* case of obviousness has not been established.

CLAIM 4

Claim 4 is rejected in view of the references discussed above in connection with claims 1, 7, and 11 and additionally in view of Bogen et al. (P/N 6,281,004). The arguments made above with regard to those references and the claim limitations in common with claim 4 are incorporated by reference herein.

Claim 4 recites steps of unattendedly micro dissecting as described above and also recites providing a set of coded micro dissected section sample holders, each having a code indicating a unique tissue space coordinate in the multidimensional morphological spatial matrix of image data, and transferring each section sample to a coded micro dissected section sample holder having a code indicating the location of a transferred microdissected sample in the multidimensional morphological spatial matrix of image data.

Bogen describes a system for quality control of reagents utilized to test tissue samples. Small spots of different concentrations of a soluble antigen are located on spatially discrete regions of a matrix. When testing the reagent, different spots will have different colors to indicate the sensitivity of the reagent. (4:5-21).

It is stated in the Office Action, at page 15, that Bogen describes microscopic slides with tissue sections containing labels containing surgical accession numbers, patient name, and a bar code (col. 7, last paragraph) which represents a coded tissue section sample holder.

As described above, the samples affixed to the matrix in Bogen are different concentrations of antigens utilized to test the sensitivity of a reagent and have no relationship to a spatial image of any kind. The codes assigned relate to identifying the patient and surgery for which the quality control step was performed. Accordingly, the disclosure of Bogen is unrelated to the claimed feature relating to indicating the location of a micro dissected sample section in the multidimensional morphological spatial matrix of image data. Further, Lemelson describes assigning coordinate values to certain features located by a scanning device such as MRI. There is no disclosure relating to assigning codes to actual micro dissected section samples indicating the location of the section samples in a multidimensional spatial matrix.

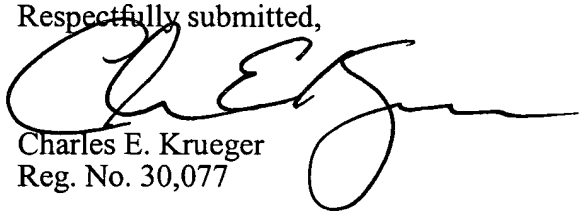
Accordingly, none of the references disclose the steps recited in independent claim 4 and a *prima facie* case of obviousness has not been established.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (925) 944-3320.

Respectfully submitted,



Charles E. Krueger
Reg. No. 30,077

LAW OFFICE OF CHARLES E. KRUEGER
P.O.Box 5607
Walnut Creek, CA 94596
Tel: (925) 944-3320 / Fax: (925) 944-3363

CLAIM APPENDIX
(Claims as presented in the attached Rule 116(b)(2) amendment)

1. A method for creating a multidimensional morphological reconstruction of biological tissue data characterizing biological tissue comprising the steps of:

cutting histologically thin sections of said biological tissue to produce first and second sets of alternating serial sections of said biological tissue;

mapping image data obtained from the first set of alternating serial sections onto a tissue space coordinate system to construct a multidimensional morphological tissue space matrix of image data of the first set of alternating serial sections;

unattendedly micro dissecting each serial section in the second set of alternating serial sections into a set of micro dissected section sample;

assigning a unique code to each micro dissected section sample micro dissected from the second set of alternating serial sections to form a set of coded micro dissected section samples, with each unique code indicating tissue space coordinates of each coded micro dissected section sample in the morphological tissue space matrix;

analyzing each coded micro dissected section sample to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample; and

spatially mapping the biological data characterizing each coded micro dissected section sample, micro dissected from the second set of alternating serial sections, onto the multidimensional morphological tissue space matrix, constructed from the first set of alternating serial sections and superimposing the biological data of the coded micro dissected section sample upon volume image data indicated by the code assigned to the coded micro dissected section sample.

2. The method of claim 1 where said step analyzing comprises the act of:

analyzing an incised section sample utilizing a monoclonal antibody binding to determine levels of proteins and other ligands.

3. The method of claim 1 where said step of analyzing comprises the act of:

analyzing a micro dissected section sample with a micro array to determine levels of mRNA.

4. A method for creating a multidimensional morphological reconstruction of gene expression activity in a biological tissue sample comprising the steps of:

cutting histologically thin sections of said sample to produce first and second sets of alternating serial sample sections;

histologically-staining and coverslipping said first set of serial sample sections for light microscopy;

constructing a multidimensional morphological spatial matrix of image data from the first set of histologically-stained serial sample sections;

mounting and covering the second set of serial sample sections with a micro dissection membrane;

unattendedly micro dissecting each of the second set of serial sample sections into a plurality of micro dissected section samples;

providing a set of coded micro dissected section sample holders, with each coded micro dissected section sample holder having a code indicating a unique tissue space coordinate in the multidimensional morphological spatial matrix of image data;

transferring each micro dissected section sample to a coded micro dissected section sample holder having a code indicating the location of a transferred micro dissected section sample in the multidimensional morphological spatial matrix of image data;

analyzing each coded micro dissected section sample to obtain biological gene expression data;

spatially superimposing gene expression data of a micro dissected section sample onto ~~the~~ a spatial coordinate of the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample holder holding the micro dissected section sample.

6. The method of claim 4 further comprising the step of:

generating displays correlating values of biological data with locations in the 3-D (three-dimensional) visualization.

7. A method for creating a multidimensional morphological reconstruction of biological data characterizing a biological tissue sample comprising the steps of:

cutting histologically thin sections of said biological tissue sample to form a set of serial sample sections;

constructing a multidimensional morphological spatial matrix of image data from the set of serial sample sections of said biological tissue sample;

unattendedly micro dissecting each serial section of said biological tissue sample into a multidimensional spatial matrix of coded micro dissected section samples, with a code assigned to a coded micro dissected section sample indicating the location of the coded micro dissected section sample in the multidimensional spatial matrix;

analyzing each coded micro dissected section sample to obtain biological data characterizing the coded micro dissected section sample; and

linking the biological data characterizing each coded micro dissected section sample to the location in the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample.

9. The method of claim 7 where:

each coded micro dissected section sample is a specific multidimensional volume image data element of the multidimensional morphological spatial matrix of image data from said biological tissue sample, and where each such coded micro dissected section sample contains all of the tissue used to produce said volume image data.

10. The method of claim 7 where:

each coded micro dissected section sample is a specific range of multidimensional volume image data from the multidimensional morphological spatial matrix of image data from said biological tissue sample.

11. A system for creating a multidimensional morphological reconstruction of biological data characterizing a biological tissue sample comprising:

means for cutting histologically thin sections of said biological tissue sample to form a set of serial sample sections;

means for constructing a multidimensional morphological spatial matrix of image data from the set of serial sample sections of said biological tissue sample;

means for unattendedly micro dissecting each serial section of said biological tissue sample into a multidimensional spatial matrix of coded micro dissected section samples, with a code of a coded micro dissected section sample indicating the location of the coded micro dissected section sample in the multidimensional spatial matrix;

means for analyzing each coded micro dissected section sample to obtain biological data characterizing the coded micro dissected section sample; and

means for linking the biological data characterizing each coded micro dissected section sample to the location in the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample.